The pathogenesis of pulmonary hypertension - an update

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Abstract: Elevation of the mean pulmonary arterial pressure to 25 mm Hg within the low-pressure system of the pulmonary circulation is defined as pulmonary hypertension. Pulmonary hypertension may be the consequence of various clinical and pathophysiological entities. Many of these conditions, however, result in a final common pathway of pathogenesis. This pathway is characterised by the triad of excessive vasoconstriction, microthrombosis and remodelling of pulmonary arteries. Remodelling is arguably the most important factor: its complex pathogenesis is not completely understood and no specific treatment directly targets vascular remodelling. This article aims to review the current understanding of the pathogenesis of pulmonary hypertension and to give insights in future developments in this evolving field.

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The pathogenesis of pulmonary hypertension – an update

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Summary

Elevation of the mean pulmonary arterial pressure to ≥25 mm Hg within the low-pressure system of the pulmonary circulation is defined as pulmonary hypertension. Pulmonary hypertension may be the consequence of various clinical and pathophysiological entities. Many of these conditions, however, result in a final common pathway of pathogenesis. This pathway is characterised by the triad of excessive vasoconstriction, microthrombosis and remodelling of pulmonary arteries. Remodelling is arguably the most important factor: its complex pathogenesis is not completely understood and no specific treatment directly targets vascular remodelling. This article aims to review the current understanding of the pathogenesis of pulmonary hypertension and to give insights in future developments in this evolving field.

Key words: *pulmonary hypertension; pathogenesis; vasoconstriction; microthrombosis; vascular remodelling; bone morphogenetic protein receptor type II (BMPR2)*

Introduction

Pulmonary hypertension is an umbrella term [1] used for many different conditions that are all defined by an increase of the mean pulmonary arterial pressure (mPAP) to 25 mm Hg or more [2]. About 30 entities that result in such pulmonary pressure elevation are recognised by the World Health Organization classification of pulmonary hypertension [3]. Based on clinical and pathophysiological features, these entities are further divided into five groups. Group 1, pulmonary arterial hypertension (PAH), includes the idiopathic and hereditary forms in addition to disease associated with predisposing conditions, such as infection with human immunodeficiency virus, liver cirrhosis, connective-tissue disease and congenital heart disease. PAH induced by the use of drugs (e.g. anorexigenic agents) is also included in this group. Group 2 is classified as pulmonary hypertension due to left-sided heart disease; Group 3 includes hypoxia-induced elevations of the pulmonary pressure and pulmonary hypertension associated with lung disease; Group 4 includes those where chronic thromboembolic events result in an increase of the pulmonary pressure. Lastly, Group 5 is pulmonary hypertension due to miscellaneous disorders that, pathophysiologically, cannot be attributed to one distinct group (for example pulmonary hypertension in the context of sarcoidosis or myeloproliferative disorders).

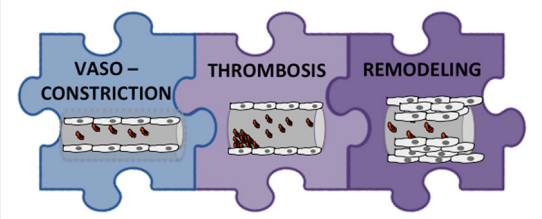

Figure 1

The three pieces in the pathogenesis of pulmonary hypertension. Pure vasoconstriction occurs in early disease; microthrombotic events are observed at increasing frequency during evolution of the disease; remodelling of the small pulmonary arteries is arguably the most important factor.

Most studies in the field, independent of whether they were designed for pharmaceutical interventions or to address experimental questions, have been conducted in PAH, which is an orphan disease (the worldwide incidence rate of PAH is difficult to estimate, registry data report incidence rates of 1–7 cases per million [4, 5]). The development of PAH and, moreover, both its aggravation and acceleration, is thought to be mediated by the combination of genetic variants that predispose an individual to develop PAH, and a second factor such as inflammatory activity and/or infection which than triggers the onset of active disease [6]. Interestingly, gender appears to play a key role in disease risk, with premenopausal women having a two- to fourfold higher risk of developing PAH than men. However, upon disease diagnosis, females have a more favourable prognosis than men and also show a better response to vasodilator therapy [7, 8]. In contrast to the predominance of female patients in the clinic, experimental data from animal models suggest that female animals are, at least in part, protected from the development of pulmonary hypertension by the effects of oestrogen [9]. This phenomenon is referred to as the "oestrogen paradox" or "sexual dimorphism" of pulmonary arterial hypertension.

There are three major pathogenetic features of PAH – vasoconstriction, microthrombotic events and vascular remod-

elling of the small pulmonary arteries (fig. 1) – which are not exclusive to this disease but are present in most forms of pulmonary hypertension.

This article aims to discuss the current developments in our understanding of the three major pathogenetic factors in pulmonary hypertension.

Vasoconstriction

Vasoconstriction of pulmonary arteries is an essential factor in the pathogenesis of pulmonary hypertension and, when present without microthrombosis and vascular remodelling, probably represents an early and potentially reversible stage in the development of the disease. This is reflected by the fact that vasoresponders (i.e. patients who show a substantial reduction of the mPAP of >10 mm Hg below a value of 40 mm Hg upon inhalation of vasoactive compounds) have an excellent prognosis when treated with calcium channel blocking agents [10, 11]. Moreover, several cardiopulmonary reflexes mediate pulmonary pressure elevation by vasoconstriction upon distinct triggers such as hypoxia (hypoxic pulmonary vasoconstriction or Euler-Liljestrand reflex) and left atrial hypertension (Hermo-Weiler or Kitaev reflex) (reviewed in [12]). Hypoxia also decreases the expression of potassium channel proteins and results in depolarisation of the membrane of pulmonary artery smooth muscle cells. These mechanisms, in turn, induce calcium influx and calcium release from intracellular stores, resulting in smooth muscle cell contraction [13]. The pathogenetic role of ion channels has been emphasised by a recent study that identified mutations in *KCNK3* (potassium channel subfamily K, member 3) ("channelopathies") in patients with hereditary PAH [14].

Vasoconstriction is mainly mediated by an imbalance of vasoactive factors, i.e. an excess of vasoconstrictors and a concomitant deficiency of vasodilating mediators. Three major pathways have been described for this, through the action of prostacyclins, endothelin-1 and nitric monoxide [15], all of which have been found to be dysregulated in pulmonary hypertension. For example, 20 years ago, Giaid and coworkers described decreased expression levels of endothelial nitric oxide synthase in patients with PAH compared with controls [16], which suggests a reduced bioavailability of the potent vasodilator nitric oxide (NO) and its second messenger cyclic guanine monophosphate (cGMP). In addition, in patients with pulmonary hypertension with concurrent chronic haemolysis or sickle cell disease, it has been found that the release of arginase from erythrocytes leads to degradation of arginine, which is an important substrate for NO [17]. Current therapies address the shortage of NO by decreased degradation of cGMP through inhibition of phosphodiesterase-5 or, conversely, by increased cGMP production through stimulation of the soluble guanylate cyclase. Similarly, the levels of vasoreactive prostacyclins and their second messenger cAMP (cyclic adenosine monophosphate) are reduced in patients with PAH [18]. This, at least in part, might be explained by a decreased expression of prostacylin synthase in lung tissue of patients with PAH [19]. Endothelin-1 is one of the most potent endogenous vasoconstrictors [20]. Increased levels of endothelin-1 were detected in lung tissue of PAH patients and circulating protein levels were found to be higher than in controls [21]. Of note, these levels were found to correlate with the severity of pulmonary pressure elevation [22]. Endothelin-1 acts through endothelin-A and -B receptors which are located on endothelial (ET1-B) and vascular smooth muscle cells (ET1-A and -B). Vasoconstriction is mainly mediated by ET1-A receptors whereas ET1-B receptors have been described as neutralising circulating Endothelin-1 [23]. However, the development of selective antagonists against ET1-A receptors has not resulted in better clinical results as compared with dual receptor blockade.

The important role of all three pathways involved in vasoconstriction is highlighted by the clinical success of PH-targeted therapies [24]. However, it is important to note that while these therapies have been shown to improve dramatically symptoms and quality of life of PAH patients, none of them cure the disease.

Thrombosis

Microthrombotic events play an important role in the evolution of PAH. Such events are observed at increasing frequency in older patients with longstanding disease. Several coagulopathies have been described in patients with PAH, including protein C and S deficiency (resulting in reduced endogenous anticoagulation) and increased von Willebrand factor activity (resulting in increased procoagulatory activity) [25, 26]. However, since many coagulation factors are acute-phase proteins and inflammation is an emerging concept in the pathogenesis of pulmonary hypertension [27], it remains unclear whether the observed alterations in the expression of coagulation factors are of true pathogenetic relevance. Experimental studies in animal models of the disease have recently suggested an active role for the coagulation factor Xa (FXa) [28]. As such, direct inhibition of FXa by the application of rivaroxaban was more effective in preventing right ventricular hypertrophy as compared with warfarin or placebo. However, no data exist on the use of novel oral anticoagulants in PAH patients. The only prospective study to date conducted to elucidate the role of oral anticoagulation has found a survival benefit in patients with idiopathic PAH when treated with coumarins. In all other forms of PAH the results were inconclusive [29]. For the prevention of microthrombotic events, we think that in the absence of clear contraindications, the use of oral anticoagulation is supported by the importance of this pathogenetic concept not exclusively in idiopathic forms but also in other patients with PAH.

Remodelling

Remodelling is a key factor in the pathogenesis of PAH and, during recent years, has been associated with a neoplastic-like process. Such a notion is supported by several mechanisms involved in vascular remodelling, such as uncontrolled proliferation, altered metabolism, clonal expansion, somatic instability and resistance to programmed cell death [30]. Remodelling might involve both arterial and venous components of the pulmonary vascular bed: In small pulmonary arteries (<300 um), remodelling is char-

acterised by excessive proliferation of cells in all vascular layers (fig. 2), in particular by uncontrolled proproliferative activity of smooth muscle cells. Remodelling of venules is less well defined, but may be prominently observed in pulmonary venoocclusive disease and in postcapillary pressure elevation due to left-sided heart disease [31].

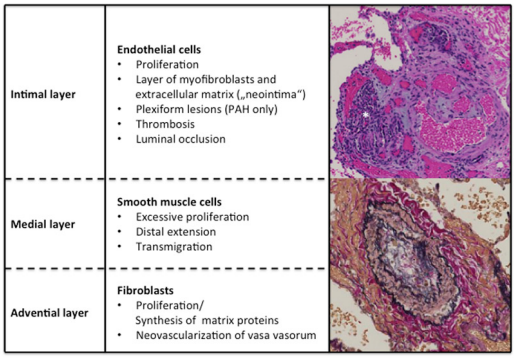

Figure 2

Features of pulmonary artery vascular remodelling in different cell types. All vascular cell types (endothelial cells, smooth muscle cells and adventitial fibroblasts) are involved in pulmonary artery remodelling and are characterised by excessive proliferation. The accumulation of myofibroblasts and extracellular matrix proteins within the endothelial layer is termed "neointima". Plexiform lesions (shown by white star) are a system of thin-walled, dilated vessels as consequence of endothelial proliferation. These lesions are found exclusively in pulmonary arterial hypertension (PAH). The most prominent changes are observed within the vessel's medial layer and mediated by a imbalance between proproliferative and apoptotic activity of smooth muscle cells and transmigration of these cells and myofibroblasts in the endothelial layer. Within the adventitial layer, neovascularisation of vasa vasorum and increased production of matrix proteins is observed (shown by Elastin-Van Gieson (EVG) staining). These alterations result in excessive hyperplasia, increased vessel thickness and luminal occlusion (reviewed in [70]).

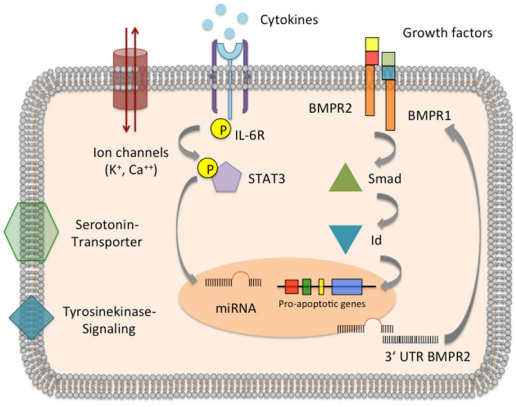

Figure 3

Overview of important factors in pulmonary vascular remodelling. BMPR2 is expressed on pulmonary artery smooth muscle cells and is the master regulator in remodelling of pulmonary arteries. Upon binding of ligands, BMPR2 and BMPR1 dimerise and activate proapoptotic genes through the action of the transcription factors Smad and Id (inhibitor of differentiation). Dysregulation of this pathway, for example due to mutations in *BMPR2*, results in a proproliferative state. Inflammatory cytokines (e.g. interleukin-6 [IL-6]) phosphorylate the transcription factor STAT3 and induce the expression of miRNAs. MicroRNAs act as gene silencers and downregulate BMPR2, which directly inhibits cell cycle regulators. Ion channels, serotonin transporters and receptors associated with tyrosine kinase signalling are also involved in mediating vasoconstriction and remodelling.

Anecdotal reports have described substantial improvement of PAH patients when treated with tyrosine kinase inhibitors (in particular with imatinib) resulting in "cure", or weaning of intravenous vasoactive therapy [32, 33]. A small recent study has confirmed these findings and suggested improvement of functional class and quality of life in patients treated with imatinib [34]. Improvement under this therapy is attributed to antiproliferative activity and "reverse remodelling". However, no pathological examination has confirmed such effects and, moreover, tyrosine kinase inhibitor therapy is limited by lack of specificity and substantial adverse effects [35, 36]. To date, no PH-targeted therapy addresses vascular remodelling, which remains the Achilles heel in the long-term treatment of PAH patients and, still, defines chronicity, progression and incurability of the disease.

The pathogenesis of remodelling is not completely understood and is mediated by a plethora of growth factors, mitogens, cytokines, ion channels, receptors, neurotransmitters, viruses and transcription factors [37, 38]. This is shown in simplified form in figure 3. One of the hallmark factors within this complex network is the bone morphogenetic protein receptor type II (BMPR2), a member of the transforming growth factor-beta superfamily. BMPR2 is arguably the most investigated and, so far, the most important regulator of vascular remodelling of pulmonary arteries. BMPR2 is expressed on pulmonary endothelial and vascular smooth muscle cells. Upon binding of specific ligands (in particular BMP-2 and also BMP-4), BMPR2 heterodimerises with BMPR1 resulting in activation of Smad and Id (inhibitor of differentiation) proteins. These downstream signalling events activate master regulators of cell cycle control (e.g. p21 or CDKN1A) and, in turn, inhibit proliferation, activate apoptosis and induce cell senescence. In 70% of patients with hereditary PAH and in as much as 20% of patients with idiopathic PAH, loss-of-function mutations in the *BMPR2* gene have been identified [39, 40] and many of these are gene rearrangement or *de-novo* mutations [41, 42]. Moreover, nongenetic dysregulations of BMPR2 are observed in many secondary forms of PAH – including hypoxia-induced pulmonary hypertension [43, 44], pulmonary hypertension associated with systemic sclerosis [45], chronic heart failure [46], congenital heart disease [46, 47] and human immunodeficiency virus infection [48]. In all of these diseases, the protein expression of BMPR2 is reduced. Of interest, regulation of BMPR2 signalling is also controlled by endothelin-1 [49], which might provide an interesting link between vasoconstriction and remodelling. Evidence suggests that dysfunctional BMPR2 results in the imbalance of proliferation and apoptosis, which, in turn, leads to vascular remodelling.

Mutations in *BMPR2* were first identified in PAH patients 15 years ago and, to date, more than 20 disease-relevant mutations have been identified [40]. Hereditary PAH also includes mutations in other disease-relevant genes, for example mutations in the activin receptor-like kinase-1 (ALK-1) [50] or, as mentioned above, in the gene coding

for the potassium channel KCNK3 [14] (reviewed in [31]). However, mutations within the BMPR2 gene are the most common and dysregulations of BMPR2 resulting in functional defects make BMPR2 to an interesting pathogenetic and therapeutic target beyond identifiable genetic aetiologies of the disease. The reason for the downregulation of BMPR2 in nongenetic entities is not clear. We and others have provided a mechanistic explanation for the dysregulation of BMPR2 and, by the identification of specific microRNAs, set off the "era of noncoding RNAs in pulmonary hypertension" [51, 52]. Noncoding RNAs include housekeeping RNAs (for example, ribosomal RNA and transfer RNA), small noncoding RNAs (with a length of fewer than 200 nucleotides), and long noncoding RNAs (>200 nucleotides) [53]. Since these RNA fragments have no encoding function they have long been discarded as genetic "junk" [54]. Within the last few years, however, noncoding RNAs have emerged as important gene silencers in many diseases including respiratory disorders [55, 56], and it is estimated that more than 60% of the human genome is under the regulatory control of these noncoding RNAs – of which microRNAs (miRNAs) are the most investigated to date [57].

MicroRNAs are composed of 18–22 nucleotides and, following a complex biogenesis, bind as single stranded RNA through Watson-Crick base pairing to the mRNA sequence of a target gene. This binding process triggers either the truncation of the targeted mRNA or the translation of mRNA into protein without affecting mRNA stability. As such, miRNAs act as post-transcriptional gene silencers. In the aftermath of the initial description of miRNAs with pulmonary hypertension [58], a plethora of papers has been published on this topic. In our opinion, the most important miRNAs involved in PAH pathogenesis are those derived from the cluster miR-17-92, which have been shown to downregulate the expression of *BMPR2*. As such, these miRNAs can provide a mechanistic explanation for the observed dysregulation of this protein in the development of pulmonary vascular remodelling. Of note, the miRNA cluster miR-17-92 has been found to be controlled by inflammatory cytokines, in particular by the acute-phase reactant interleukin-6 (IL-6) [58]. Elevated levels of IL-6 have been described in patients with idiopathic pulmonary arterial hypertension [59, 60] and in patients with pulmonary hypertension due to chronic obstructive pulmonary disease [61], chronic haemolysis in sickle cell disease [62] and pulmonary hypertension due to liver cirrhosis [63]. Stimulation of pulmonary arterial endothelial cells with IL-6 resulted in activation of the transcription factor STAT3 (signal transducer and activator of transcription) followed by subsequent induction of miR-17-92 expression. This, in turn, was shown to reduce levels of BMPR2. Of interest, constitutional activation of STAT3 was found in distinct lesions of the vessel wall of patients with pulmonary arterial hypertension [64]. This ongoing activation of STAT3 might result in continuous induction of miRNAs and BMPR2 downregulation. Conversely, antagonism of these miRNAs by oligonucleotides ("antagomiRs") resulted in functional restoration of BMPR2 both *in vitro* and *in vivo* [65, 66]. In animals carrying *BMPR2* mutations, similar effects were achieved by genetic transfection of functional BMPR2 [67]. These data emphasise the important role of a functional STAT3-miRNA-BMPR2 pathway to prevent the development of vascular remodelling within the pulmonary circulation. Which specific components of the BMPR2 gene and its pathway will serve as therapeutic target in a translational setting remains to be determined.

Inflammation is another emerging concept in the pathobiology of vascular remodelling and includes the complex interaction between humoral and cellular factors triggered by infectious, toxic and autoimmune events. Cellular factors include the accumulation of T and B lymphocytes, monocytes and plasma cells within the vessel wall and surrounding tissue of patients with pulmonary hypertension [27, 68]. Moreover, many cytokines have been found to be dysregulated in the context of pulmonary hypertension, many with unknown pathogenic relevance. However, levels of several cytokines have been found to predict outcome of the disease and, as prognostic markers, were more accurate than haemodynamic parameters [60]. An elegant experimental study has recently highlighted the important interaction between inflammation and BMPR2 status by showing that defective BMPR2 signalling might induce the production of inflammatory cytokines such as IL-6 and IL-8 in pulmonary arterial smooth muscle cells [69]. However, it remains undetermined whether dysregulated BMPR2 or increased levels of inflammatory cytokines are the initial trigger of these events or, conversely, whether both factors might augment one another within the vicious circle of pulmonary vascular remodelling.

Conclusions

The pathogenesis of pulmonary hypertension is driven by the triad of vasoconstriction, microthrombosis and remodelling of small pulmonary arteries. All of these factors, although to a different extent, are present in most entities that result in elevation of the pulmonary pressure. Vascular remodelling is the most important and, to date, the least treatable factor. As such, remodelling is the factor that still defines pulmonary hypertension as a chronic and incurable disease. Most of our understanding of pulmonary arterial remodelling has been provided by insights into the regulation and function of the growth factor receptor BMPR2. Dysfunctional BMPR2 signalling is the major driving force for a proproliferative and antiapoptotic state of vascular cells. Targeted therapies with genetic vehicles and synthetic oligonucleotides have shown promising results in experimental and preclinical studies. Such therapies, however, are still far from implementation in clinical practice.

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Figures (large format)

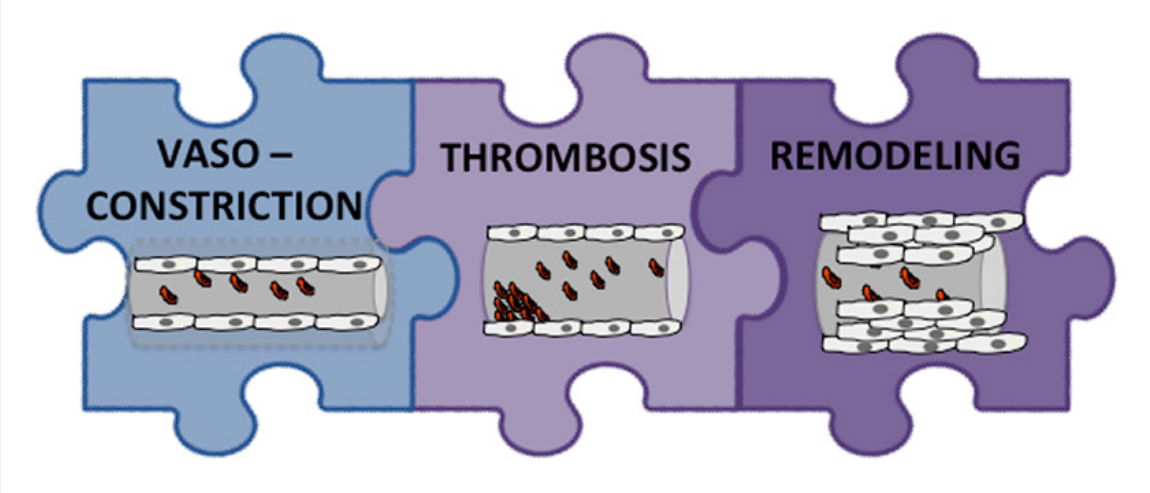

Figure 1

The three pieces in the pathogenesis of pulmonary hypertension. Pure vasoconstriction occurs in early disease; microthrombotic events are observed at increasing frequency during evolution of the disease; remodelling of the small pulmonary arteries is arguably the most important factor.

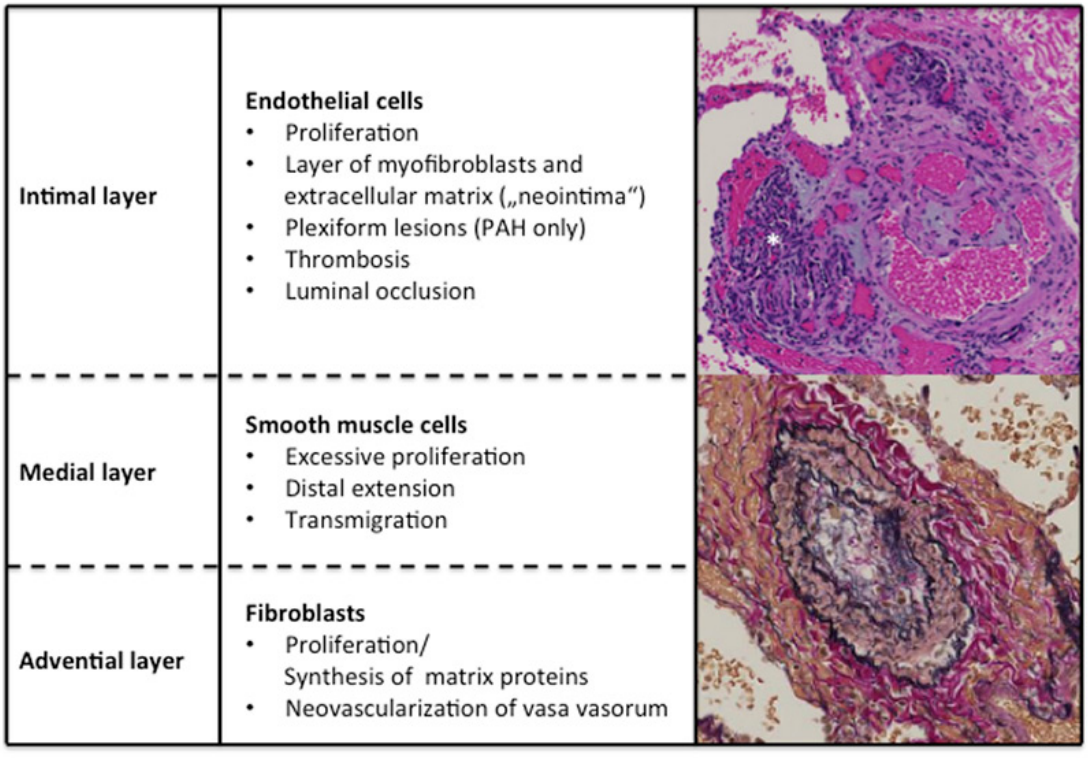

Figure 2

Features of pulmonary artery vascular remodelling in different cell types. All vascular cell types (endothelial cells, smooth muscle cells and adventitial fibroblasts) are involved in pulmonary artery remodelling and are characterised by excessive proliferation. The accumulation of myofibroblasts and extracellular matrix proteins within the endothelial layer is termed “neointima”. Plexiform lesions (shown by white star) are a system of thin-walled, dilated vessels as consequence of endothelial proliferation. These lesions are found exclusively in pulmonary arterial hypertension (PAH). The most prominent changes are observed within the vessel’s medial layer and mediated by a imbalance between proproliferative and apoptotic activity of smooth muscle cells and transmigration of these cells and myofibroblasts in the endothelial layer. Within the adventitial layer, neovascularisation of vasa vasorum and increased production of matrix proteins is observed (shown by Elastin-Van Gieson (EVG) staining). These alterations result in excessive hyperplasia, increased vessel thickness and luminal occlusion (reviewed in [70]).

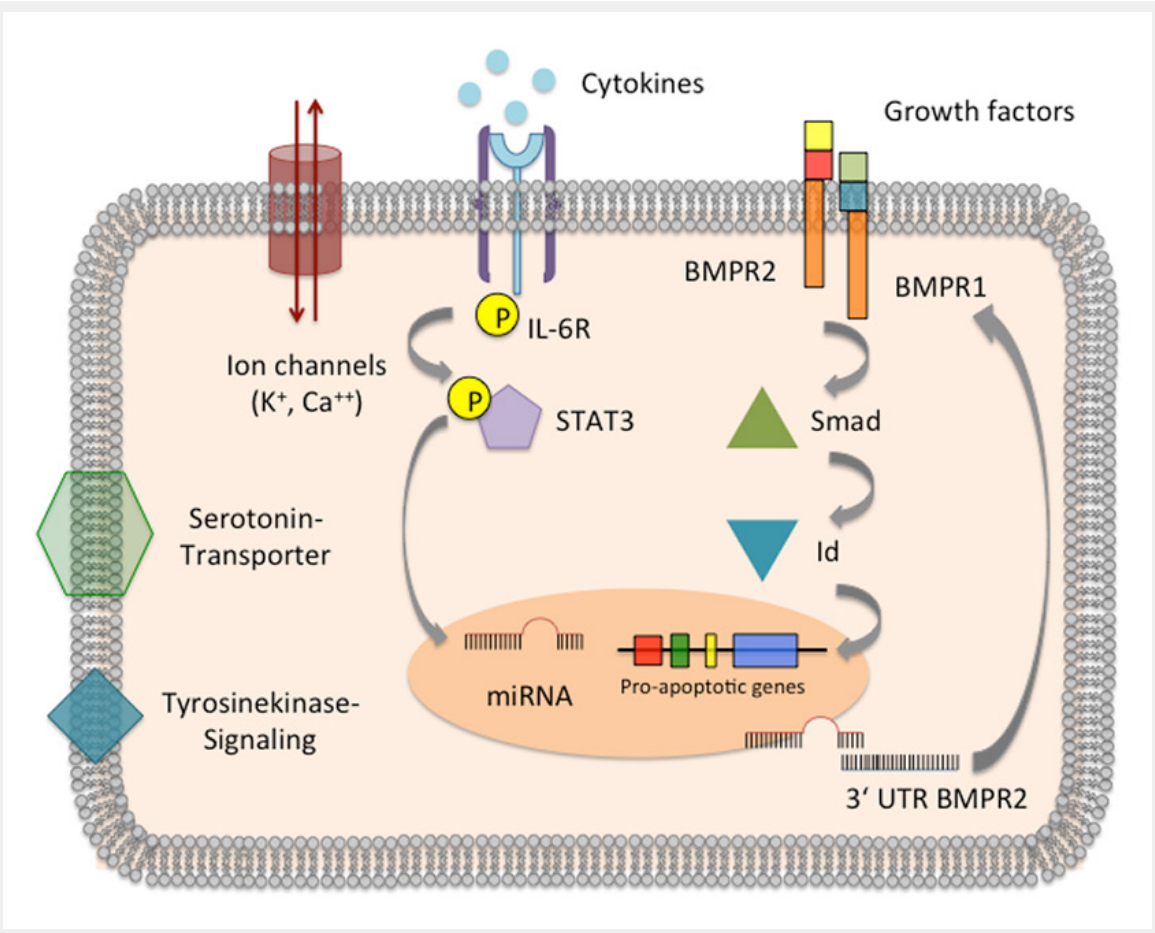

Figure 3

Overview of important factors in pulmonary vascular remodelling. BMPR2 is expressed on pulmonary artery smooth muscle cells and is the master regulator in remodelling of pulmonary arteries. Upon binding of ligands, BMPR2 and BMPR1 dimerise and activate proapoptotic genes through the action of the transcription factors Smad and Id (inhibitor of differentiation). Dysregulation of this pathway, for example due to mutations in *BMPR2*, results in a proproliferative state. Inflammatory cytokines (e.g. interleukin-6 [IL-6]) phosphorylate the transcription factor STAT3 and induce the expression of miRNAs. MicroRNAs act as gene silencers and downregulate BMPR2, which directly inhibits cell cycle regulators. Ion channels, serotonin transporters and receptors associated with tyrosine kinase signalling are also involved in mediating vasoconstriction and remodelling.